Does refractory rheumatoid arthritis status matter in modeling patient global assessment (PtGA) trajectories over 20 years in a large US registry?

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Refractory RA, defined only by treatment, was associated with worse PtGA over time in comparison to non-refractory patients. The two distinct trajectories support a reRA definition independent of disease activity.

BACKGROUND

- Refractory rheumatoid arthritis (reRA) is characterized by an inadequate response to multiple DMARDs.
- Many factors including environment, comorbidities, socio-demographics, and the treatment itself influence poor treatment response.
- **Objective:** Accounting for these factors, we sought to identify the impact of having refractory RA on the trajectory of patient global assessments (PtGA) over time.

METHODS

- Participants with RA from the Forward databank were followed between 1999 and 2019. ReRA was defined as the use of a third advanced therapy with at least one TNFi and a non-TNFi biologic (nTNFi) or JAKi.
- Participants with RA, stratified into reRA and non-reRA cohorts, were matched based on age, sex, disease duration, and follow-up time to becoming refractory.
- Patients were followed from initiation of the first biologic until the last observation (each case/control was matched until the first one was lost to follow-up).
- Demographics, patient-reported outcomes (PROs), comorbidities, and treatment were characterized at several time points during the study, from baseline, when the participants met the refractory criteria and at the end of follow-up.
- Mixed-effect regression models with random slopes were analyzed using PtGA (rated 0, [VERY WELL], to 10,[VERY POOR]) as the outcome. Akaike information criterion (AIC) was used to identify the best model when adjusting for time, sociodemographic, comorbidities, and treatment (concomitant and initial biologic).

RESULTS

- After matching, 1,384 participants were included in the study (692 in each group).
- The matched sample had a mean age of 57 (SD 11) years old, 88% female, 92% white, and had a mean of 14 years of education.
- From the initiation of the first biologic to the last observation, the reRA group was characterized by increased obesity, higher comorbidities, and worse PROs than matched controls.
- These measures increased over time for both groups (Table 1).
- The distribution of first biologic was: TNFi (89.5%), nTNFi (9.5%), and JAKi (1%).
- Best model was described in Figure 1 by the AIC criterion. Even after controlling for all the factors, ReRA was associated with an increase of 0.49 in PtGA over follow-up when compared to non-reRA patients.
- Selected in the model: concomitant fibromyalgia criteria (estimated coefficient 0.95), depression (0.23), lung problems (0.17), use of opioids (0.35), glucocorticoids (0.23) and first biologic as nTNFi (0.30) were all associated with worsening PtGA over time (except education (-0.15)), but irrespective of being reRA (the interactions were not statistically significant).

Table 1. Characterization of reRA vs matched controls at 3 moments in time: initiation of first biologic, when reRA criteria were met, and at last observation (mean (SD), except when indicated otherwise).

	Initiation of first biologic		reRA criteria first met		End of follow up§	
Mean (SD)	Non-reRA	ReRA	Non-reRA	ReRA	Non-reRA	ReRA
Demographics						
Follow-up time, years median (IQR)	0		5.5 (3 - 9)		8.0 (5 -12.5)	
Hx smoking, %	49.7	50.3	51.9	53.3	52.3	53.9
BMI, kg/m²	28.0 (7.2)	28.4 (6.4)	28.1 (7.4)	28.8 (6.7)	28.1 (7.4)	28.7 (6.7)
Obese, BMI ≥ 30, %	30.0	34.0	30.7	35.7	30.1	35.4
RA duration, years	14.5 (10.3)	14.4 (10.7)	20.5 (11.3)	20.4 (11.6)	23.1 (11.5)	23.0 (11.7)
Patient-Reported Outcomes						
Pain VAS, 0-10	3.5 (2.7)	4.3 (2.8)	3.7 (2.8)	4.5 (2.6)	3.9 (2.8)	4.5 (2.7)
Fatigue VAS, 0-10	4.2 (2.9)	4.8 (3.0)	4.5 (3.1)	5.1 (2.9)	4.4 (3.1)	5.2 (2.9)
PtGA VAS, 0-10	3.4 (2.5)	4.0 (2.5)	3.7 (2.5)	4.4 (2.3)	3.8 (2.6)	4.5 (2.4)
HAQ-II, 0-3	1.0 (0.7)	1.1 (0.7)	1.0 (0.8)	1.2 (0.7)	1.1 (0.8)	1.2 (0.7)
PAS-II, 0-10	3.4 (2.2)	4.0 (2.1)	3.6 (2.3)	4.3 (2.0)	3.8 (2.3)	4.4 (2.1)
Comorbidities						
RDCI, 0-9	1.4 (1.4)	1.7 (1.5)	1.9 (1.6)	2.1 (1.7)	2.1 (1.7)	2.2 (1.6)
Hx pulmonary disorder, %	28.3	26.4	43.2	45.1	50.0	51.0
Hx cardiac disorder, %	17.3	19.4	32.2	32.7	40.4	40.5
Hx fracture, %	16.2	16.8	27.5	31.6	34.4	38.5
Hx depression, %	38.8	41.1	52.2	55.1	56.4	59.4
Hx diabetes, %	9.5	10.4	18.7	18.4	24.1	23.1
Hx cancer, %	16.2	14.5	29.9	25.1	38.1	31.7
Hx GI disorder, %	50.5	57.9	66.8	74.4	71.8	78.6
Fibromyalgia 2016 criteria, %	22.5	28.2	23.2	32.9	21.7	29.4
Concomitant Medications						
Glucocorticoids, %	40.1	46.1	33.0	47.0	32.6	42.8
csDMARD, %	84.6	85.7	70.8	71.8	66.6	68.3
NSAID, %	64.8	61.6	43.3	43.8	37.1	38.5
Any opioid, %	24.2	31.7	30.0	38.0	30.0	36.7

§ For each matched pair, the end of follow-up was considered the last observation or the time when one was lost to follow-up, whichever came first.
Highlighted in bold when P<0.05 (T-tests or Chi-squared tests when appropriate)
Hx = History; VAS = Visual Analog Scale; PtGA = Patient Global Assessment; HAQ-II = Health Assessment Questionnaire-II; PAS-II = Patient Activity Scale-II; RDCI = Rheumatic Disease Comorbidity Index.

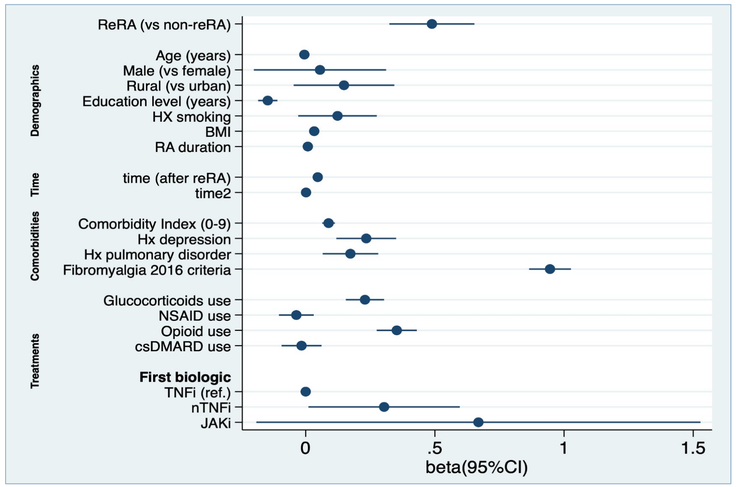

Figure 1. Coefficients (95%CI) of the final mixed-effect regression model with random slopes for Patient Global Assessment

CONCLUSION

- These findings show that even after accounting for several factors contributing to PtGA over time, having refractory RA (defined by only treatment use) is still highly associated with worse PtGA.
- This shows the possible value of having a reRA definition agnostic to disease activity as these two groups had distinct trajectories over time.
- Future work is also needed to identify and quantify the impact of the factors contributing to worse trajectories of PtGA score and other outcomes for those who are refractory compared to controls.

FORWARD
The National Databank for Rheumatic Diseases

Abstract ID 1331